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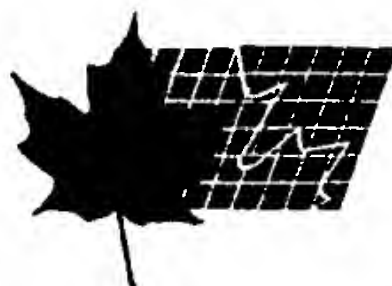
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Ottawa Hull K1A 0C9

(21) (A1) 2,163,175
(22) 1995/11/17
(43) 1996/05/31

(51) Int.Cl. ⁶
C07D 307/68; C07D 307/30; C07D 309/32; C07D 319/12;
C07D 327/06; C07D 263/34; C07D 277/56; C07D 207/34;
C07D 333/38; C07C 333/08; A61K 31/27; A61K 31/33

(19) (CA) **APPLICATION FOR CANADIAN PATENT** (12)

(54) Anti-Viral Aromatic O-Alkylated Oximes, Esters and Thioethers

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(30) (US) 08/346,819 1994/11/30

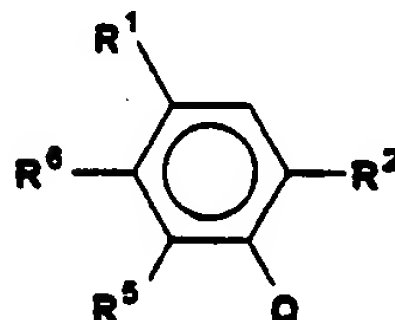
(57) 20 Claims

Notice: This application is as filed and may therefore contain an incomplete specification.



ABSTRACT

Compounds of the formula



wherein Q is $\begin{array}{c} -C=NOR^4 \\ | \\ R^3 \end{array}$ or $-XR'$;

X is oxygen or sulphur;

R¹ is hydrogen, halogen, C₁-C₄ alkyl or C₁-C₄ alkoxy;

R² is hydrogen, halogen, C₁-C₄ alkyl, C₁-C₄ alkoxy, C₃-C₄ alkenyloxy, C₃-C₄ alkynyloxy, mono-, di- or tri-halomethyl, trifluoromethoxy, C₁-C₄ alkylthio, C₃-C₄ branched alkylthio, nitro, or cyano;

R³ is hydrogen or C₁-C₄ alkyl;

R⁴ is C₃-C₆ alkenyl, C₃-C₆ alkynyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxyalkyl, C₁-C₆ alkylthioalkyl, C₁-C₆ hydroxyalkyl, C₁-C₆ acyloxyalkyl, C₁-C₆ aroyloxyalkyl, C₁-C₆ carboxyalkyl, C₁-C₆ alkylcarboxyalkyl, C₆-C₁₂ arylcarboxyalkyl, C₁-C₆ aminoalkyl, C₁-C₆ alkylaminoalkyl, C₁-C₆ dialkylaminoalkyl, C₁-C₆ trialkylsilylalkyl, wherein each of the aforementioned alkyl moieties may be straight-chain or branched; C₃-C₆ cycloalkyl, C₁-C₆ alkylphenyl, C₇-C₁₂ arylalkyl, C₇-C₁₂ alkarylalkyl, or heterocyclylalkyl, wherein the heterocyclic moiety is morpholinyl, piperidinyl, pyrrolidinyl, piperazinyl, oxiranyl, oxetanyl, furanyl, tetrahydropyranyl or tetrahydrofuranyl;

R' is C₁-C₆ haloalkyl, C₁-C₆ alkoxyalkyl, C₁-C₆ alkylthioalkyl, C₁-C₆ hydroxyalkyl, C₁-C₆ acyloxyalkyl, C₁-C₆ aroyloxyalkyl, C₁-C₆ aminoalkyl, C₁-C₆ alkylaminoalkyl, C₁-C₆ dialkylaminoalkyl, C₁-C₆ trialkylsilylalkyl, wher in each f the aforementioned

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alkyl moieties may be straight-chain or branched; C₁-C₆ alkylphenyl, C₇-C₁₂ arylalkyl, C₇-C₁₂ alkarylalkyl, or heterocyclylalkyl, wherein the heterocyclic moiety is morpholinyl, piperidinyl, pyrrolidinyl, piperazinyl, oxiranyl, oxetanyl, furanyl, tetrahydropyranyl or tetrahydrofuranyl;

R⁵ is hydrogen, halo, methyl, mono-, di- or tri-halomethyl; and

R⁶ is an aliphatic or cyclic side chain as defined herein.

These compounds are useful for inhibiting the growth or replication of retroviruses such as HIV.

ANTI-VIRAL AROMATIC O-ALKYLATED OXIMES,
ETHERS AND THIOETHERS

5 Field of the Invention

 This invention relates to novel aromatic O-alkylated oximes, ethers and thioethers. In particular, this invention relates to novel aromatic O-alkylated oximes, ethers and thioethers useful as anti-viral agents. More particularly, this invention relates to novel aromatic O-alkylated oximes, ethers and thioethers useful as agents against certain retroviruses such as the members of the group of Human Immunodeficiency Viruses (HIV).

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Background of the Invention

 Retroviruses are viruses whose replication requires the transcription of viral RNA into DNA using the viral reverse transcriptase molecules attached to the viral RNA. This reverse transcription is the opposite of normal transcription which makes RNA from DNA.

 Known retroviruses include HIV-1, HIV-2, the herpes family of viruses, HTLV-1 and cytomegalovirus (CMV). HIV, the virus which is presently believed to cause acquired immunodeficiency syndrome (AIDS), is considered one of the principle threats to human life and health worldwide.

 Various anti-HIV compounds have been proposed as useful in the treatment and prevention of AIDS, e.g., zidovudine (AZT), didanosine (ddI), zalcitabine (ddC), nevirapine, and dextran sulfate. However, none of the proposed compounds have been proven to be totally effective in the treatment or prevention of AIDS. For example, the three currently FDA approved compounds for the treatment of AIDS, i.e., AZT, ddI and ddC, can all cause undesirable side effects in a patient, such as inhibition of bone marrow cell growth, and their effectiveness is limited by virus mutation.

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 U.S. Patent No. 5,268,389 describes certain

thiocarboxylate ester compounds useful for inhibiting the growth or replication of HIV.

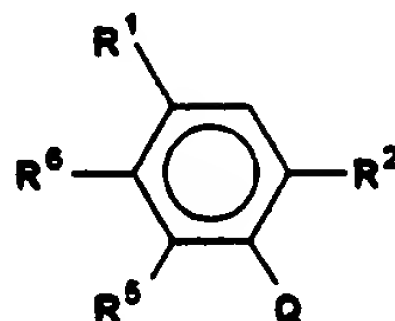
It is the purpose of this invention to provide novel aromatic O-alkylated oximes, ethers and thioethers, useful as anti-viral agents.

It is also the purpose of this invention to provide a method for inhibiting or preventing the growth or replication of human immunodeficiency viruses using the novel aromatic O-alkylated oximes, ethers and thioethers.

Finally, it is also the purpose of this invention to provide compositions useful for inhibiting or preventing the growth or replication of human immunodeficiency viruses, comprising the novel aromatic O-alkylated oximes, ethers and thioethers.

Description of the Invention

This invention relates to a compound of the formula



(I)

wherein Q is -C=NOR^4 or -XR^4 ;



X is oxygen or sulphur;

R¹ is hydrogen, halogen, C₁-C₄ alkyl or C₁-C₄ alkoxy;

R² is hydrogen, halogen, C₁-C₄ alkyl, C₁-C₄ alkoxy, C₃-C₄ alkenyloxy, C₃-C₄ alkynyloxy, mono-, di- or tri-halomethyl, trifluoromethoxy, C₁-C₄ alkylthio, C₃-C₄ branched alkylthio, nitro, or cyano;

R³ is hydrogen or C₁-C₄ alkyl;

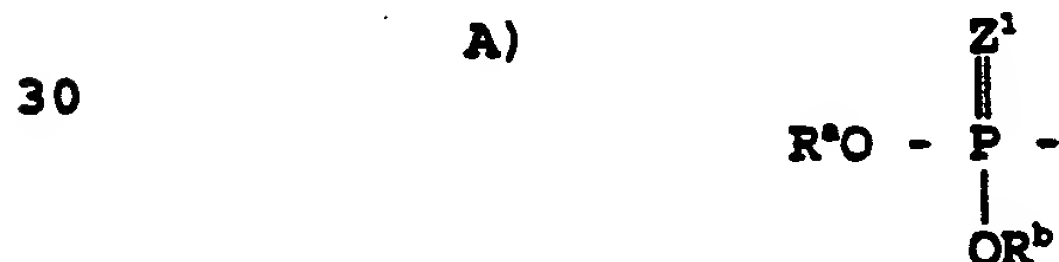
R' is C₃-C₆ alkenyl, C₃-C₆ alkynyl, C₁-C₆ haloalkyl,
 C₁-C₆ alkoxyalkyl, C₁-C₆ alkylthioalkyl, C₁-C₆ hydroxyalkyl,
 C₁-C₆ acyloxyalkyl, C₁-C₆ aroyloxyalkyl, C₁-C₆ carboxyalkyl,
 C₁-C₆ alkylcarboxyalkyl, C₆-C₁₂ arylcarboxyalkyl, C₁-C₆
 5 aminoalkyl, C₁-C₆ alkylaminoalkyl, C₁-C₆ dialkylaminoalkyl,
 C₁-C₆ trialkylsilylalkyl, wherein each of the
 aforementioned alkyl moieties may be straight-chain or
 branched; C₃-C₆ cycloalkyl, C₁-C₆ alkylphenyl, C₇-C₁₂
 arylalkyl, C₇-C₁₂ alkarylalkyl, or heterocyclalkyl,
 10 wherein the heterocyclic moiety is morpholinyl,
 piperidinyl, pyrrolidinyl, piperazinyl, oxiranyl,
 oxetanyl, furanyl, tetrahydropyranyl or
 tetrahydrofuranyl;

R' is C₁-C₆ haloalkyl, C₁-C₆ alkoxyalkyl, C₁-C₆
 15 alkylthioalkyl, C₁-C₆ hydroxyalkyl, C₁-C₆ acyloxyalkyl,
 C₁-C₆ aroyloxyalkyl, C₁-C₆ aminoalkyl, C₁-C₆
 alkylaminoalkyl, C₁-C₆ dialkylaminoalkyl, C₁-C₆
 trialkylsilylalkyl, wherein each of the aforementioned
 alkyl moieties may be straight-chain or branched; C₁-C₆
 20 alkylphenyl, C₇-C₁₂ arylalkyl, C₇-C₁₂ alkarylalkyl, or
 heterocyclalkyl, wherein the heterocyclic moiety is
 morpholinyl, piperidinyl, pyrrolidinyl, piperazinyl,
 oxiranyl, oxetanyl, furanyl, tetrahydropyranyl or
 tetrahydrofuranyl;

25 R⁵ is hydrogen, halo, methyl, mono-, di- or
 tri-halomethyl;

R⁶ is

1) R² - NH -, wherein R² is



35 wherein R^a and R^b are independently hydrogen or C₁-C₆
 alkyl; and Z¹ is O or S; r



wherein Z^2 is O or S; and

R^A is:

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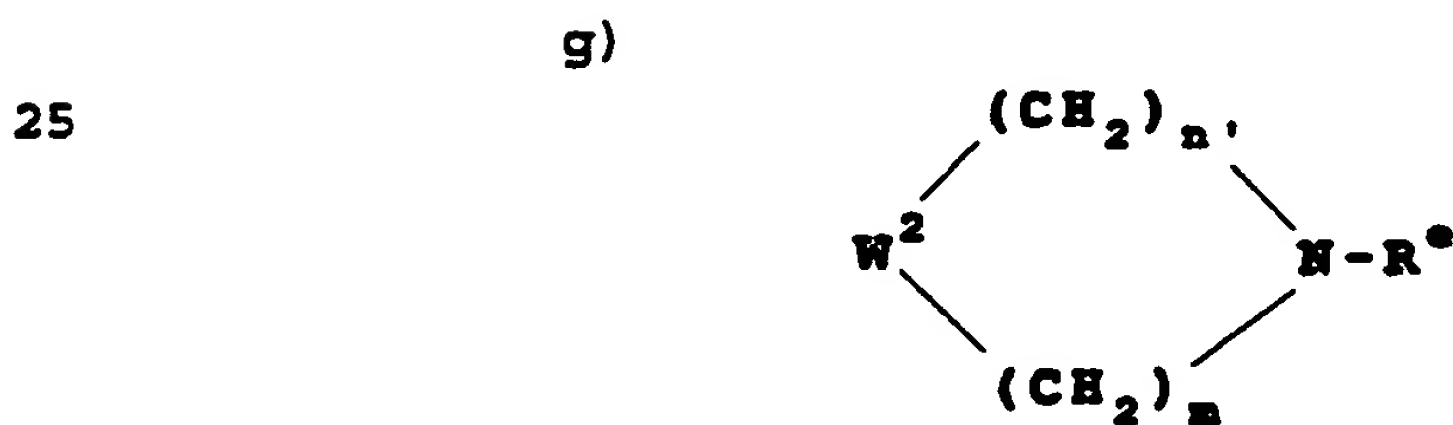
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- a) fully unsaturated, partially or fully reduced or substituted oxathiinyl, furanyl, dithiinyl, dioxinyl, thienyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, thiadiazolyl, pyrazolyl, pyrrolyl, imidazolyl, pyranyl, oxathiazinyl, oxadiazolyl, or indolyl;
- b) substituted or unsubstituted, linear or branched C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 alkoxy, C_2-C_8 alkenyloxy, C_2-C_8 alkynloxy, or C_1-C_8 mono- or di-alkylamino; C_3-C_7 cycloalkyl, C_3-C_7 cycloalkyl C_1-C_8 alkyl, C_3-C_7 cycloalkenyl, unsubstituted or substituted by C_1-C_8 alkyl or C_7-C_8 phenylalkyl; or
- c) aryl, aralkyl, aryloxyalkyl, or cycloalkylaryloxy wherein each alkyl moiety contains from 1 to 10 carbon atoms and each aryl moiety is naphthyl, phenyl or phenyl substituted by one or more halo, C_1-C_8 alkyl, carboxyl, C_1-C_8 haloalkyl, C_1-C_8 alkylthio, phenyl, nitro, amino, C_1-C_8 alkoxycarbonylamino, hydroxyl, acetyl, acetyloxy, phenoxy, C_1-C_8 alkoxycarbonyl or C_1-C_8 alkylcarbonyl;
- (d) $R^7 - W -$, wherein W is O, NH or NR^f wherein R^f is C_1-C_8 alkyl; and R^7 is linear or branched, unsubstituted

5 or halo-substituted C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkenyl, C₃-C₆ cycloalkyl C₁-C₆ alkyl, C₃-C₆ cycloalkenyl unsubstituted or substituted by C₁-C₆ alkyl, unsubstituted phenyl or phenyl substituted by halo, C₁-C₆ alkyl, C₁-C₆ alkoxy, carboxyl, C₁-C₆ alkythio, phenyl, nitro, amino, hydroxyl, acetyl, acetyloxy, phenoxy, C₁-C₆ alkoxycarbonyl, or C₁-C₆ alkylcarbonyl; 10 furanylalkyl, tetrahydrofuranylalkyl, oxetanylalkyl, or oxiranylalkyl;

15 e) R⁸ - W¹ - R⁹, wherein R⁹ is a linear or a branched C₁-C₆ alkylidene; W¹ is O or S; and R⁸ is linear or branched C₁-C₄ alkyl;

20 f) R⁹ R¹⁰ - N - R⁹, wherein R⁹ is as defined above; and R⁹ and R¹⁰ are independently linear or branched C₁-C₄ alkyl;



30

wherein

R⁹ is as defined above; W² is O, S, NH, NR¹¹ or CR¹²R¹³; wherein R¹¹ is linear or branched C₁-C₄ alkyl; R¹² and R¹³ are independently hydrogen or linear or branched C₁-C₄ alkyl; and 35

n' and m are independently 1, 2 or 3;

h) $R^{14}-O_2-C-R^e$, wherein

R^e is as defined above; and R^{14} is linear or branched C_1-C_6 alkyl, C_3-C_6 alkenyl, or C_3-C_6 alkynyl; or C_3-C_7 cycloalkyl, C_3-C_7 cycloalkyl C_1-C_6 alkyl, or C_3-C_7 cycloalkenyl, unsubstituted or substituted by C_1-C_6 alkyl;

i) $U-R^e-$, wherein

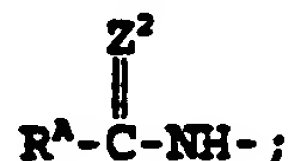
R^e is as defined above; U is hydroxyl, acyl oxy, aryloxy, arylsulphonyloxy, nitro, cyano or trimethylsilyl;

j) 1-adamantyl, 2-adamantyl or bornyl;

k) $Ar^1 - R^e -$, wherein

R^e is as defined above; and Ar^1 is phenyl or phenyl substituted independently with one to three halogen, mono-, di- or tri- halomethyl, nitro, C_1-C_4 alkyl, C_3-C_4 alkenyl, C_1-C_4 alkyloxy, C_3-C_4 alkenyloxy, or C_3-C_4 alkynyloxy.

Preferred compounds are those compounds wherein R^6 is



Z^2 is O or S; and

R^A is

a) fully unsaturated, partially or fully reduced or substituted oxathiinyl, furanyl, dithiinyl, dioxinyl, thienyl, thiazoyl, oxazoyl, isoxazoyl, isothiazoyl, thiadiazolyl, pyrazolyl, pyrrolyl, pyranyl, oxathiazinyl, or oxadiazolyl;

b) linear or branched C₁-C₈ alkyl, C₃-C₈ alkenyl, C₃-C₈ alkynyl, C₁-C₈ alkoxy, C₃-C₈ alkenyloxy, C₃-C₈ alkynloxy, or C₁-C₈ mono- or di- alkylamino; C₃-C₈ cycloalkyl or C₃-C₈ cycloalkenyl;

5 c) phenyl or phenyl substituted by one or more halo, C₁-C₈ alkyl, C₁-C₈ haloalkyl, C₁-C₈ alkylthio, phenyl, amino, hydroxyl, carboxyl, acetyl, acetyloxy, C₁-C₈ alkoxycarbonyl, C₁-C₈ alkylcarbonyl or phenoxy; C₇-C₈ phenylalkyl or C₇-C₈ phenoxyalkyl.

10 More preferred are those compounds wherein R^A is

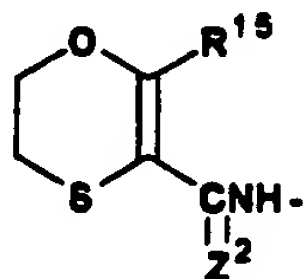
a) dihydro-3-oxathiinyl, furanyl, dihydrofuranyl, thienyl, pyrrolyl, dihydro-2-dithiinyl, or dihydro-2-dioxinyl, which can be substituted by one to three C₁-C₄ alkyl or C₁-C₄ alkoxyalkyl groups;

15 b) linear or branched C₁-C₈ alkyl, C₂-C₈ alkenyl, C₃-C₈ alkynyl, C₁-C₈ alkoxy, C₃-C₈ alkenyloxy, C₃-C₈ alkynyloxy or C₁-C₈ mono- or di-alkylamino; C₃-C₈ cycloalkyloxy or C₃-C₈ cycloalkenyloxy; or

20 c) phenyl or phenyl substituted by one or more halo, C₁-C₈ alkyl, C₁-C₈ haloalkyl, C₁-C₈ alkylthio, carboxyl, amino, C₁-C₈ alkoxycarbonyl, hydroxyl, C₁-C₈ alkylcarbonyl, phenyl or phenoxy.

Particularly preferred are those compounds wherein R⁶ is

25



Z² is O or S;

30 R¹ is hydrogen; fluoro; or methyl;

R² is hydrogen, chloro, fluoro, or methyl;

R³ is hydrogen or methyl;

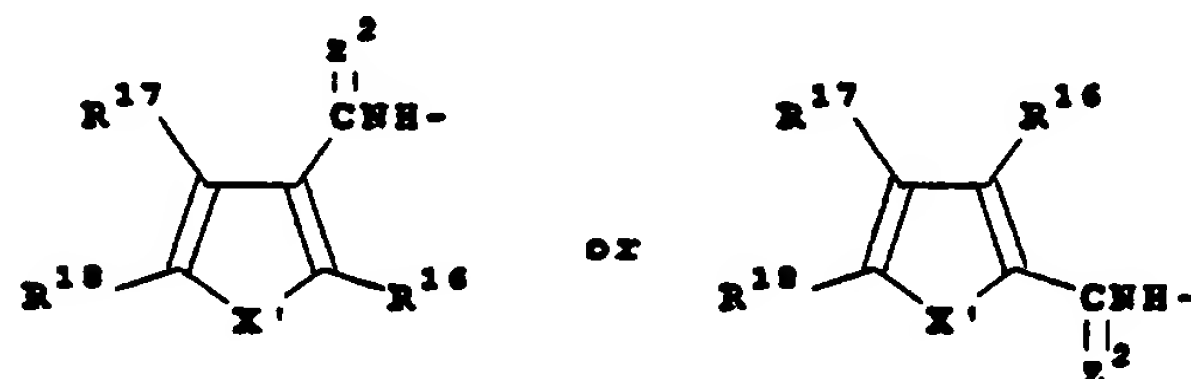
R⁴ is cyclopentyl or cyclohexyl;

R⁵ is hydrogen; and

35 R¹⁵ is methyl, ethyl or propyl.

Additionally preferred compounds are the furan, thiophene and pyrrole derivatives of the compound of formula I wherein R^6 is:

5



10

Z^2 is O or S;

X^1 is O, S, NH or N-methyl,

R^{16} is hydrogen, methyl, ethyl,

1,1-dimethylethyl, fluoro, chloro, carboxyl, acetamido, cyano, C_1 - C_6 alkylthio, C_1 - C_6 haloalkoxy, C_1 - C_6 acyloxy,

15

(C_1 - C_6 alkoxy)carbonyl, or (C_1 - C_6 alkyl)carbonyl; and

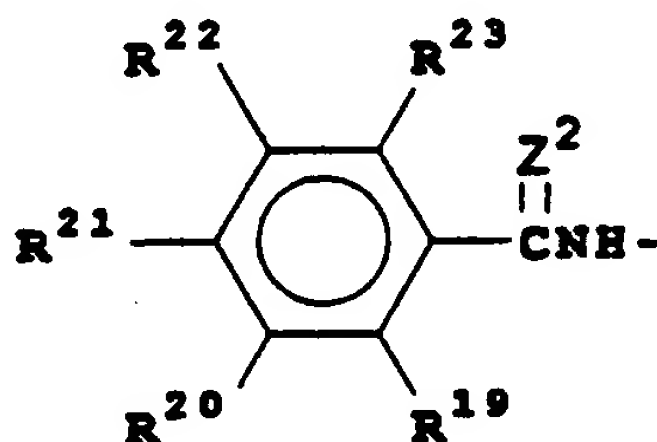
R^{17} and R^{18} are independently hydrogen or methyl.

More preferred furan, thiophene and pyrrole derivatives are those wherein R^1 , R^3 and R^5 are hydrogen, R^2 is halogen, R^4 is C_3 - C_6 alkenyl or C_3 - C_6 alkynyl, which can be linear, branched or cyclic, and Z^2 is S.

20

Also preferred are the compounds of formula I wherein R^6 is:

25



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Z^2 is O or S;

R^{19} , R^{20} , R^{21} , and R^{22} are independently hydrogen or halogen, preferably hydrogen; and

35

R^{23} is hydrogen, halogen, C_1 - C_4 alkyl, C_1 - C_4 alkoxy, mono, di- or tri-haloalkoxy, C_1 - C_4 hal alkyl, C_1 - C_4 alkylthio, amino, C_1 - C_4 alkylcarbonylamino, hydroxyl,

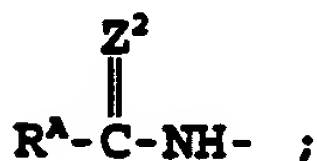
acetyl, acetyloxy, or acetylamino, preferably hydrogen, methyl, ethyl, chloro, iodo, amino, bromo, fluoro, methylthio, methoxy, difluoromethoxy, or hydroxy.

Also preferred as compounds of this invention are the derivatives of acyclic carboxamides or carbamates of the compound of formula I wherein X, Z², R¹, R², R³, R⁴ and R⁵ are as recited above for formula I and R⁶ is



wherein R^A is a linear or branched C₃-C₆ alkyl, C₃-C₆ alkenyl, C₁-C₆ alkoxy, C₃-C₆ alkenyloxy, C₃-C₆ alkynyloxy, C₃-C₆ mono- or di-alkylamino, or C₃-C₆ alkynyl; phenyl, C₇-C₈ phenylalkyl, C₇-C₈ phenoxyalkyl, C₃-C₇ cycloalkyl, or C₃-C₇ cycloalkenyl.

More preferred compounds are the compounds of formula I wherein R¹ is hydrogen or fluoro; R⁴ is C₃-C₆ alkenyl or C₃-C₆ alkynyl, which may be linear, branched or cyclic; R⁶ is



R^A is a linear or branched C₃-C₆ alkyl, C₃-C₆ alkenyl, C₃-C₆ alkynyl, C₃-C₆ alkoxy, C₃-C₆ alkenyloxy or C₃-C₆ alkynyloxy; C₇-C₈ phenylalkyl, C₇-C₈ phenoxyalkyl, C₃-C₆ cycloalkyl, or C₃-C₇ cycloalkenyl.

Especially preferred compounds of this invention are the compounds of formula I wherein R¹-R⁵ are hydrogen; R⁴ is C₃-C₆ alkenyl or C₃-C₆ alkynyl, which may be linear, branched or cyclic; R⁶ is



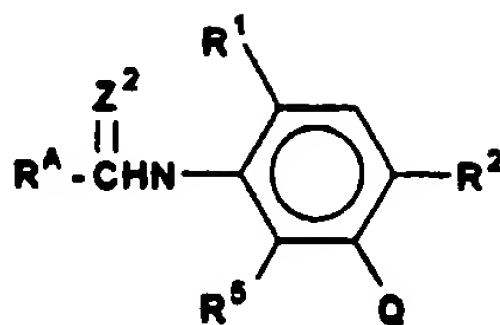
R^A is a linear or branched C₃-C₆ alkyl, C₃-C₆ alkoxy, C₃-C₆ alkenyloxy, C₃-C₆ alkynyloxy, C₃-C₆ cycloalkyl, or C₃-C₆ cycloalkenyl.

The compounds of this invention are useful for the inhibition of the growth or replication of retroviruses, particularly human immunodeficiency viruses such HIV-1, in vitro and in vivo. The compounds are useful in the therapeutic or prophylactic treatment of diseases caused by retroviruses, such as acquired immune deficiency syndrome or an HIV infection in a human or other mammal.

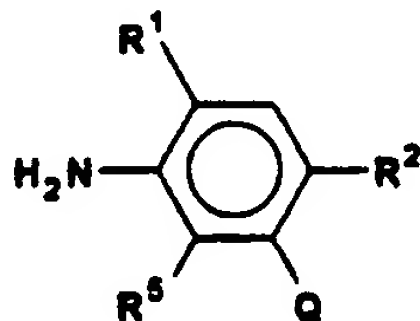
It is intended that the scope of this invention encompass all isomers, including positional or stereoisomers, of any compound of formula I exhibiting isomerism. It is also intended that any novel processes or intermediates for synthesizing said compounds be included within the scope of this invention.

GENERAL SYNTHETIC METHODS

Compounds of formula



wherein Z^2 is O and R^A is oxathiinyl, furanyl, thienyl, pyrrolyl, other heterocyclyl, or substituted phenyl, can be prepared from the appropriate carboxylic acid, R^A -COOH, and an aniline derivative, i.e;



by employing one of the methods known in the art of amide bond formation. For example, the carboxylic acid can be converted to an acid halide, such as the acid chloride,

$R^A\text{COCl}$, which can then be reacted with the aniline derivative to form the amide. The amide forming reaction is carried out in an appropriate solvent, such as methylene chloride, toluene, methyl ethyl ketone, tetrahydrofuran, dimethylformamide or acetonitrile, at a temperature of about 0°C to about 100°C .

It is usually preferable to carry out the reaction in the presence of a base, such as triethylamine or pyridine. Other reactive derivatives of the carboxylic acid can be employed: for example the anhydride of the carboxylic acid or a mixed anhydride, such as alkoxycarbonyloxy derivative, can be reacted with the aniline derivative. Alternatively, the carboxylic acid and aniline derivative can be reacted directly in the presence of a condensing agent such as dicyclohexylcarbodiimide to form the amide.

The aniline derivatives can be prepared by reduction of the corresponding nitro compounds by well-known methods, for example with hydrogen and a catalyst, such as Raney nickel or platinum, or with a metal-acid combination, such as iron or tin and hydrochloric or acetic acid. Oxime ethers are made from the corresponding aldehyde by conventional methods. An exception is in the preparation of tertiary o-alkyl oximes which are made by the action of an unsubstituted oxime and a tertiary alcoholic ester under acid catalysis in a suitable solvent such as THF, dioxane or DME. A suitable acid catalyst would be hydrochloric, sulphuric or perchloric acid.

Other compounds of this invention in which R^A is an alkoxy can be prepared by reacting the appropriate aniline derivative with an alkoxycarbonyl chloride, under conditions essentially similar to those used for reaction of an acid chloride with the aniline derivative. They can also be prepared by reacting the appropriate isocyanate derivative with an alcohol. The isocyanate can be

prepared by reacting the aniline derivative or a suitable salt thereof, such as the hydrochloride, with phosgene or a phosgene substitute, such as trichloromethyl chloroformate.

5 Compounds of this invention wherein R^A is alkoxy and Z^2 is sulphur can be similarly prepared using alkoxy thiocarbonyl chloride under conditions described above or from the appropriate isothiocyanate derivative and an alcohol.

10 Thiocarboxaniliides of this invention wherein Z^2 is S and R^A is furanyl, thienyl, pyrrolyl, other heterocyclyl or substituted phenyl, can be prepared starting from the corresponding amide and reacting it with a sulfurating agent such as Lawesson's reagent or phosphorus
15 pentasulphide in a suitable solvent such as toluene, xylene, DME, pyridine, or the like.

20 The following examples are provided to illustrate the synthesis of the compounds of the present invention.

Example I

25 The following Tables 1a and 1b list representative compounds that were prepared using the methods described above.

TABLE 1a

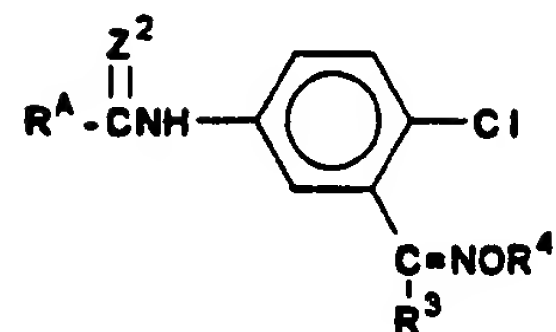


TABLE 1a					
No.	R ^A	Z ²	R ³	R ⁴	mp°C
1	2-CH ₃ -3-Puranyl	O	H	CH ₂ C≡CH	135-136
2	"	S	H	CH ₂ CH=CH ₂	88-89
3	"	S	H	CH ₂ CH=CH	79-80
4	"	S	H	CH ₂ C ₆ H ₅	131-133
5	"	S	H	CH ₂ CO ₂ C(CH ₃) ₃	130-131
6	"	S	H	C ₆ H ₅ (cyclo)	73-75

TABLE 1b

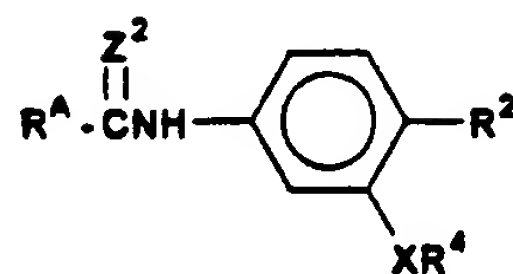


TABLE 1b						
No.	R ^A	Z ²	X	R ³	R ⁴	mp°C
7	(CH ₃) ₂ CHO	S	O	Cl	CHF ₂	110-115
8	"	S	O	Cl	COCH(CH ₃) ₂	89-91
9	"	S	O	Cl	CH ₂ COCH ₃	104-106
10	"	S	O	Cl	CH ₂ C(=NOH)CH ₃	101-105

IN VITRO SCREENING RESULTS

Representative compounds of this invention were tested for anti-viral activity by subjecting them to standard National Cancer Institute ("NCI") in vitro screening procedures. Two blanks were run with each test. The NCI test for agents active against HIV is designed to detect agents acting at any stage of the virus reproduction cycle.

In the test assay, small amounts of HIV are added to T4 lymphocyte cells. The assay measures the amount of T4 lymphocytes "killed" by HIV cytolysis. Since a complete cycle of viral reproduction is necessary to "kill" the T4 lymphocyte cells, agents that interfere with viral reproduction will protect the cells from cytolysis.

The NCI system is automated in several features to accomodate large numbers of candidate agents and is generally designed to detect anti-HIV activity. Compounds that degenerate or are rapidly metabolized in the culture conditions do not show activity in this screen. All tests are compared with at least one positive (AZT-treated) control done at the same time under identical conditions.

The Test Procedure

1) The test compound was dissolved in dimethyl sulfoxide and diluted 1:100 in cell culture medium before serial half-log₁₀ dilutions were prepared. T4 lymphocytes (CEM cell line) were then added to the cell culture medium, and, finally, after a brief interval, HIV-1 was added, resulting in a 1:200 final dilution of the test compound. Uninfected cells in the cell culture medium containing the test compound (i.e., minus HIV-1) were used as a toxicity control, and infected cells in the cell culture medium without the test compound and uninfected

cells in the cell culture medium without the test compound, were used as basic controls.

5 2) The cultures were incubated at 37°C in a 5% carbon dioxide atmosphere for 6 days.

10 3) The tetrazolium salt, XTT, was added to all wells, and the cultures were then incubated to allow formazan color development by viable cells.

15 4) Individual wells were analyzed spectrophotometrically to quantitate formazan production, and were also viewed microscopically for detection of viable cells and confirmation of protective activity.

20 5) Virus-infected cells exposed to the test compound were compared with noninfected cells exposed to the test compound, and with other appropriate controls (infected cells not exposed to the test compound and noninfected cells not exposed to the test compound, wells containing only the test compound in the cell culture medium, and so on) on the same plate. These are the first and second blanks described below.

25 6) Data were reviewed in comparison with other tests done at the same time and a determination concerning activity was made. In the first blank, HIV and T4 lymphocytes in cell culture medium, were incubated together to measure the infectivity of the virus. The viability of the cells was measured after holding for six or seven days. In an "effective" test, most cells were infected before the holding period was complete.

30 In the second blank, the T4 lymphocytes in cell culture medium and the test compound (with no HIV-1) were incubated together to measure the toxicity of the drug to the cells. The viability of the cells was measured as

a function of concentration of the compound, after incubation for seven days. The concentration of the test compound that results in 50% inhibition of cell growth is defined as its IC_{50} .

5

Finally, the protective effects of the test compounds were measured. Each cell culture and test compound were incubated with the virus and the viability of the cells was measured as a function of compound concentration after incubation for six or seven days.

10

The concentration of the test compound that results in 50% "control," i.e., a 50% reduction of the viral cytopathic effect, is defined as its EC_{50} . The therapeutic index TI_{50} was calculated as IC_{50}/EC_{50} .

15

Concentrations of test compounds required for between 20 and 50% reduction of the viral cytopathic effect can also be determined. Such compounds are classified as moderately active. Compounds with less than 20% control are considered inactive.

20

The compounds were tested to determine their reduction of HIV cytopathic effect on the human cell line CEM. Tests were done by innoculating these cell lines in-well (IW), i.e., the test compound and CEM cells were mixed on a test plate and the virus was added a short time later.

25

Screening Data for Test Compound Exhibiting Inhibition of HIV

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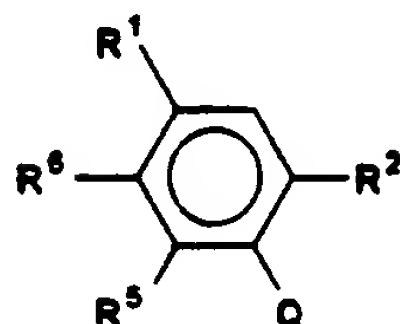
The preceding protocol was carried out with all of the compounds described above in the Examples, all of which showed some significant activity in at least one of the tests. The test results (molar) for all the tested compounds are shown in Table 2 as IC_{50} , EC_{50} and TI_{50} .

TABLE 2

Compound	IC ₅₀ (M)	EC ₅₀ (M)	TL ₅₀
1	1.60 x 10 ⁵	3.30 x 10 ⁵	5
	1.80 x 10 ⁵	3.50 x 10 ⁵	5
	>2.30 x 10 ⁵	3.90 x 10 ⁵	>6
	>2.30 x 10 ⁵	3.70 x 10 ⁵	>6
2	>1.80 x 10 ⁵	1.10 x 10 ⁵	>1400
	>1.80 x 10 ⁵	2.00 x 10 ⁵	>770
	>1.80 x 10 ⁵	4.50 x 10 ⁵	>340
	>1.80 x 10 ⁵	1.20 x 10 ⁵	>1300
3	1.60 x 10 ⁵	4.70 x 10 ⁵	340
	1.80 x 10 ⁵	3.80 x 10 ⁵	440
	>2.20 x 10 ⁵	1.30 x 10 ⁷	>170
	2.10 x 10 ⁵	1.10 x 10 ⁷	190
4	>7.10 x 10 ⁵	1.00 x 10 ⁵	>7
	>7.10 x 10 ⁵	1.60 x 10 ⁵	>4
	>7.10 x 10 ⁵	1.30 x 10 ⁵	>5
	>7.10 x 10 ⁵	1.10 x 10 ⁵	>7
5	>2.40 x 10 ⁵	2.00 x 10 ⁵	>1
	>2.40 x 10 ⁵	-	-
	1.90 x 10 ⁵	4.40 x 10 ⁵	4
	2.30 x 10 ⁵	-	-
6	>1.40 x 10 ⁵	2.50 x 10 ⁷	>58
	>1.40 x 10 ⁵	2.40 x 10 ⁷	>58
	>1.40 x 10 ⁵	1.80 x 10 ⁷	>78
	>1.40 x 10 ⁵	8.40 x 10 ⁵	>170
7	3.47 x 10 ⁵	2.62 x 10 ⁵	13
	4.64 x 10 ⁵	8.37 x 10 ⁵	6
	3.22 x 10 ⁵	-	-
	3.33 x 10 ⁵	5.78 x 10 ⁵	6
8	5.58 x 10 ⁵	-	-
	5.13 x 10 ⁵	2.80 x 10 ⁵	2
	4.17 x 10 ⁵	2.54 x 10 ⁵	2
	4.75 x 10 ⁵	1.81 x 10 ⁵	3
9	7.70 x 10 ⁵	2.70 x 10 ⁵	28
	>1.20 x 10 ⁴	2.80 x 10 ⁵	>61
	>1.20 x 10 ⁴	4.60 x 10 ⁵	>28
	>1.20 x 10 ⁴	1.10 x 10 ⁵	>110
10	1.20 x 10 ⁴	3.30 x 10 ⁵	28
	-	9.7 x 10 ⁵	-
	-	8.8 x 10 ⁵	-
	-	2.0 x 10 ⁷	-
10	-	1.6 x 10 ⁷	-
	-	-	-

What is claim d is:

1. A compound of the formula



wherein Q is $\begin{array}{c} -C=NOR^4 \text{ or } -XR' \\ | \\ R^3 \end{array}$;

5

X is oxygen or sulphur;

R¹ is hydrogen, halogen, C₁-C₄ alkyl or C₁-C₄ alkoxy;

R² is hydrogen, halogen, C₁-C₄ alkyl, C₁-C₄ alkoxy, C₃-C₄ alkenyloxy, C₃-C₄ alkynyloxy, mono-, di- or tri-halomethyl, trifluoromethoxy, C₁-C₄ alkylthio, C₃-C₄ branched alkylthio, nitro, or cyano;

10

R³ is hydrogen or C₁-C₄ alkyl;

R⁴ is C₃-C₆ alkenyl, C₃-C₆ alkynyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxyalkyl, C₁-C₆ alkylthioalkyl, C₁-C₆ hydroxyalkyl, C₁-C₆ acyloxyalkyl, C₁-C₆ aroyloxyalkyl, C₁-C₆ carboxyalkyl, C₁-C₆ alkylcarboxyalkyl, C₆-C₁₂ arylcarboxyalkyl, C₁-C₆ aminoalkyl, C₁-C₆ alkylaminoalkyl, C₁-C₆ dialkylaminoalkyl, C₁-C₆ trialkylsilylalkyl, wherein each of the aforementioned alkyl moieties may be straight-chain or branched; C₃-C₆ cycloalkyl, C₁-C₆ alkylphenyl, C₇-C₁₂ arylalkyl, C₇-C₁₂ alkarylalkyl, or heterocyclylalkyl, wherein the heterocyclic moiety is morpholinyl, piperidinyl, pyrrolidinyl, piperazinyl, oxiranyl, oxetanyl, furanyl, tetrahydropyranyl or tetrahydrofuranlyl;

15

20

25

R' is C₁-C₆ haloalkyl, C₁-C₆ alkoxyalkyl, C₁-C₆ alkylthioalkyl, C₁-C₆ hydroxyalkyl, C₁-C₆ acyloxyalkyl, C₁-C₆ aroyloxyalkyl, C₁-C₆ aminoalkyl, C₁-C₆ alkylaminoalkyl, C₁-C₆ dialkylaminoalkyl, C₁-C₆ trialkylsilylalkyl, wher in each of the aforementioned

30

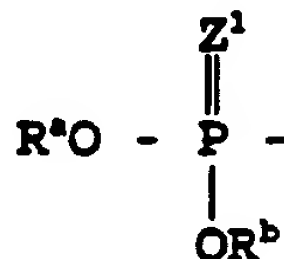
alkyl moieties may be straight-chain or branched; C₁-C₆,
alkylphenyl, C₇-C₁₂, arylalkyl, C₇-C₁₂, alkarylalkyl, or
heterocyclalkyl, wherein the heterocyclic moiety is
morpholinyl, piperidinyl, pyrrolidinyl, piperazinyl,
5 oxiranyl, oxetanyl, furanyl, tetrahydropyranyl or
tetrahydrofuranyl;

R⁵ is hydrogen, halo, methyl, mono-, di- or
tri-halomethyl; and

R⁶ is

10 1) R² - NH -, wherein R² is

A)

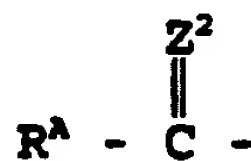


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wherein R^a and R^b are independently hydrogen or C₁-C₆,
alkyl; and Z¹ is O or S;

20

B)



wherein Z² is O or S; and

R^a is:

25

a) fully unsaturated, partially or fully
reduced or substituted oxathiinyl,
furanyl, dithiinyl, dioxinyl,
thienyl, thiazolyl, oxazolyl, isoxazolyl,
isothiazolyl, thiadiazolyl, pyrazolyl,
pyrrolyl, imidazolyl, pyranyl,
oxathiazinyl, oxadiazolyl, or indolyl;

30

b) substituted or unsubstituted, linear or
branched C₁-C₆, alkyl, C₃-C₆, alkenyl, C₃-C₆,
alkynyl, C₁-C₆, alkoxy, C₃-C₆, alkenyloxy,
C₃-C₆, alkynyloxy, or C₁-C₆, mono- or
di-alkylamino; C₃-C₇, cycloalkyl, C₃-C₆,

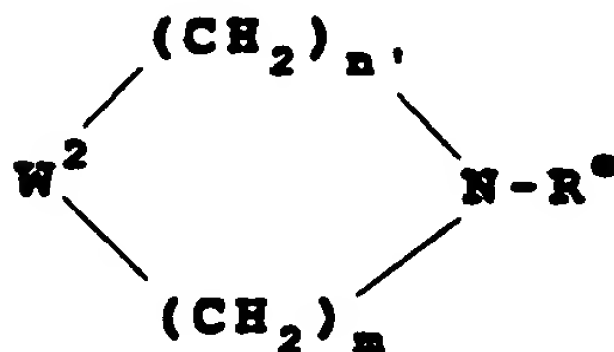
cycloalkyloxy, C₃-C₈ cycloalkylalkoxy, C₃-C₈ cycloalkyl C₁-C₆ alkyl, C₃-C₈ cycloalkenyl, unsubstituted or substituted by C₁-C₆ alkyl or C₇-C₈ phenylalkyl; or

- 5 c) aryl, aralkyl, aryloxyalkyl, or
cycloalkylaryloxy wherein each alkyl
moiety contains from 1 to 10 carbon atoms
and each aryl moiety is naphthyl, phenyl
or phenyl substituted by one or more halo,
10 C₁-C₆ alkyl, carboxyl, C₁-C₆ haloalkyl, C₁-C₆
alkylthio, phenyl, nitro, amino, C₁-C₆
alkoxycarbonylamino, hydroxyl, acetyl,
acetyloxy, phenoxy, C₁-C₆ alkoxycarbonyl or
C₁-C₆ alkylcarbonyl:
- 15 (d) R' - W -, wherein
W is O, NH or NR^f wherein R^f is C₁-C₄ alkyl;
and R' is linear or branched, unsubstituted
or halo-substituted C₁-C₆ alkyl, C₃-C₈
alkenyl, C₃-C₈ alkynyl, C₃-C₈ cycloalkyl C₁-C₆
20 alkyl, C₃-C₈ cycloalkenyl unsubstituted or
substituted by C₁-C₆ alkyl, unsubstituted
phenyl or phenyl substituted by halo, C₁-C₆
alkyl, C₁-C₆ alkoxy, carboxyl, C₁-C₆
alkylthio, phenyl, nitro, amino, hydroxyl,
25 acetyl, acetyloxy, phenoxy, C₁-C₆
alkoxycarbonyl, or C₁-C₆ alkylcarbonyl;
furanylalkyl, tetrahydrofuranylalkyl,
oxetanylalkyl, or oxiranylalkyl;
- 30 e) R^g - W¹ - R^h, wherein
R^g is a linear or a branched C₁-C₆
alkylidene;
W¹ is O or S; and
R^h is linear or branched C₁-C₄ alkyl;

- f) $R^9 R^{10} - N - R^e$, wherein
 R^e is as defined above; and R^9 and R^{10} are
independently linear or branched C_1-C_4
alkyl;

5

g)



wherein

- R^e is as defined above;
 W^2 is O, S, NH, NR^{11} or $CR^{12}R^{13}$; wherein R^{11}
is linear or branched C_1-C_4 alkyl; R^{12} and
10 R^{13} are independently hydrogen or linear or
branched C_1-C_4 alkyl; and
 n' and m are independently 1, 2 or 3;

- h) $R^{14}-O_2-C-R^e$,

wherein

15

- R^e is as defined above; and R^{14} is linear
or branched C_1-C_6 alkyl, C_3-C_6 alkenyl, or
 C_3-C_6 alkynyl; or C_3-C_7 cycloalkyl, C_3-C_7
cycloalkyl C_1-C_6 alkyl, or C_3-C_7
cycloalkenyl, unsubstituted or substituted
20 by C_1-C_6 alkyl;

- i) $U-R^e-$, wherein

R^e is as defined above; U is hydroxyl,
acyloxy, aryloxy, arylsulphonyloxy, nitro,
cyano or trimethylsilyl;

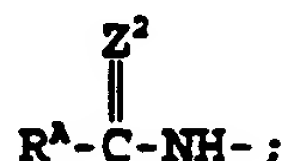
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- j) 1-adamantyl, 2-adamantyl or bornyl;

- k) $Ar^1 - R^e -$, wher in

R^6 is as defined above; and
 Ar^1 is phenyl or phenyl substituted
independently with one to three halogen,
mono-, di- or tri- halomethyl, nitro, C_1-C_4
alkyl, C_3-C_4 alkenyl, C_1-C_4 alkyloxy, C_3-C_4
alkenyloxy, or C_3-C_4 alkynyloxy.

2. A compound as recited in claim 1 wherein R^6 is



Z^2 is O or S; and

R^A is

a) fully unsaturated, partially or fully reduced or
substituted oxathiinyl, furanyl, dithiinyl, dioxinyl,
thienyl, thiazoyl, oxazoyl, isoxazoyl, isothiazoyl,
thiadiazolyl, pyrazolyl, pyrrolyl, pyranyl, oxathiazinyl,
or oxadiazolyl;

b) linear or branched C_1-C_6 alkyl, C_3-C_6 alkenyl, C_3-C_6
alkynyl, C_1-C_6 alkoxy, C_3-C_6 alkenyloxy,
 C_3-C_6 alkynyloxy, or C_1-C_6 mono- or di- alkylamino; C_3-C_6
cycloalkyl or C_3-C_6 cycloalkenyl;

c) phenyl or phenyl substituted by one or more halo,
 C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkylthio, phenyl,
amino, hydroxyl, carboxyl, acetyl, acetyloxy, C_1-C_6
alkoxycarbonyl, C_1-C_6 alkylcarbonyl or phenoxy; C_7-C_8
phenylalkyl or C_7-C_8 phenoxyalkyl.

3. A compound as recited in claim 2 wherein R^A is

a) dihydro-3-oxathiinyl, furanyl, dihydrofuranyl,
thienyl, pyrrolyl, dihydro-2-dithiinyl, or
dihydro-2-dioxinyl, which can be substituted by one to
three C_1-C_4 alkyl or C_1-C_4 alkoxyalkyl groups;

b) linear or branched C_1-C_6 alkyl, C_3-C_6 alkenyl,
 C_3-C_6 alkynyl, C_1-C_6 alkoxy, C_1-C_6 mono- or di-alkylamino,
 C_3-C_6 cycloalkyl or C_3-C_6 cycloalkenyl; r

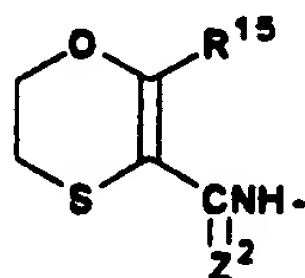
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- 23 -

c) phenyl or phenyl substituted by one or more halo, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkylthio, carboxyl, amino, C₁-C₆ alkoxy, carbonyl, hydroxyl, C₁-C₆ alkylcarbonyl, phenyl or phenoxy.

5

4. A compound as recited in claim 3 wherein R⁶ is



Z² is O or S;

R¹ is hydrogen; fluoro; or methyl;

R² is hydrogen, chloro, fluoro, or methyl;

R³ is hydrogen or methyl;

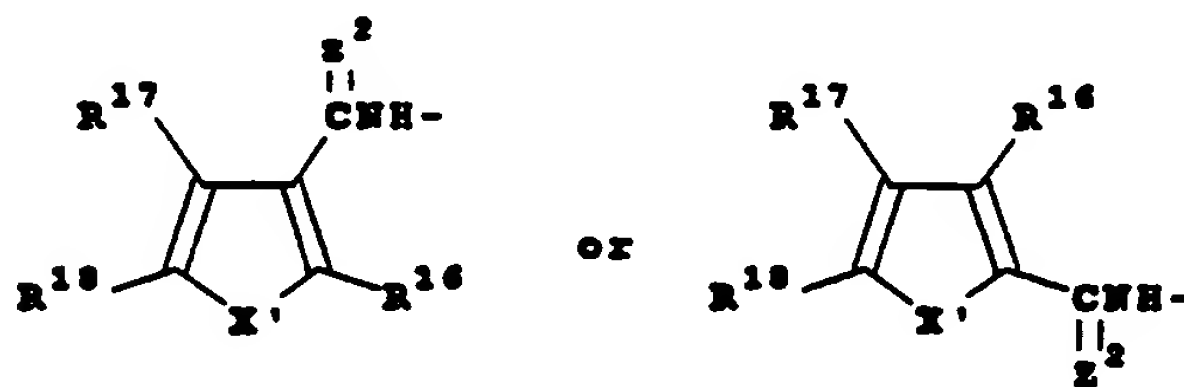
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R⁴ is cyclopentyl or cyclohexyl;

R⁵ is hydrogen; and

R¹⁵ is methyl, ethyl or propyl.

5. A compound as recited in claim 2 wherein R⁶ is:



Z² is O or S;

15

X¹ is O or S or N-methyl,

R¹⁶ is hydrogen, methyl, ethyl,

1,1-dimethylethyl, fluoro, chloro, carboxyl, acetamido, cyano, C₁-C₆ alkylthio, C₁-C₆ haloalkoxy, C₁-C₆ acyloxy, (C₁-C₆ alkoxy)carbonyl, or (C₁-C₆ alkyl)carbonyl; and

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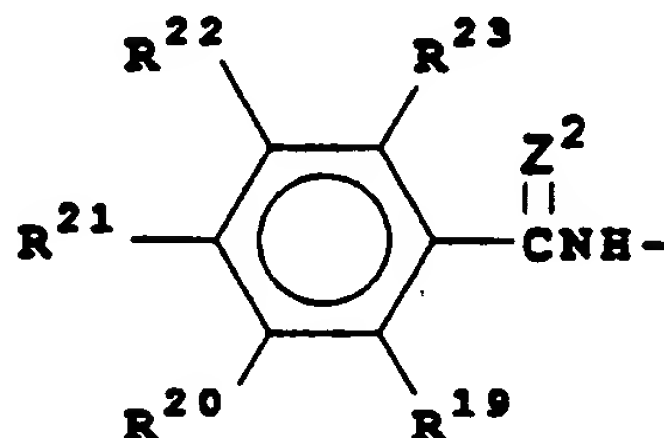
R¹⁷ and R¹⁸ are independently hydrogen or methyl.

6. A compound as recited in claim 5 wherein R¹, R³

and R^5 are hydrogen, R^2 is halogen, R^4 is C_3 - C_6 alkenyl or C_3 - C_6 alkynyl, which can be linear, branched or cyclic, and R^{16} is hydrogen, methyl, ethyl or 1,1-dimethylethyl.

7. A compound as recited in claim 2 wherein R^6 is:

5



Z^2 is O or S;

R^{19} , R^{20} , R^{21} , and R^{22} are independently hydrogen or halogen; and

10 R^{23} is hydrogen, halogen, C_1 - C_4 alkyl, C_1 - C_4 alkoxy, mono, di- or tri-haloalkoxy, C_1 - C_4 haloalkyl, C_1 - C_4 alkylthio, amino, C_1 - C_4 alkylcarbonylamino, hydroxyl, acetyl, acetyloxy, or acetylamino.

15 8. A compound as recited in claim 2 wherein R^A is a linear or branched C_3 - C_6 alkyl, C_3 - C_6 alkenyl, C_3 - C_6 alkynyl, C_3 - C_6 alkoxy, or C_3 - C_6 mono- or di-alkylamino; phenyl, C_7 - C_8 phenylalkyl, C_7 - C_8 phenoxyalkyl, C_3 - C_7 cycloalkyl, or C_3 - C_7 cycloalkenyl.

20 9. A compound as recited in Claim 2 wherein Q is $-CR^3=NOR^4$, R^A is C_1 - C_4 alkoxy, phenyl, or dihydro-3-oxathiinyl, furanyl, dihydrofuranyl or thienyl substituted by one to three methyl or ethyl groups, R^1 is H, R^2 is Cl, R^3 is H or methyl, R^4 is C_3 - C_6 carboxyalkyl or C_5 - C_7 cycloalkyl, and R^5 is H.

10. A compound as recited in Claim 9 wherein R^A is

C₁-C₄ alkoxy, Z² is S, and R³ is H.

11. A compound as recited in claim 9 wherein R^A is 2-methyl-3-furanyl, Z² is S, and R³ is H.

5 12. A compound as recited in claim 2 wherein Q is -XR', R^A is C₁-C₄ alkoxy, phenyl, or furanyl, thienyl or dihydro-3-oxathiinyl substituted by one to three methyl or ethyl groups; R² is Cl or methoxy; and R' is C₁-C₄ dihaloalkyl or C₁-C₆ alkoxyalkyl.

10 13. A method for inhibiting the growth or replication of a retrovirus in a patient infected by the retrovirus which comprises administering to the patient an effective amount of a compound as recited in claim 1.

15 14. A method as recited in claim 18 wherein the retrovirus is a HIV.

15 15. A method for inhibiting the growth or replication of a retrovirus in a patient infected by the retrovirus which comprises administering to the patient an effective amount of a compound as recited in claim 2.

20 16. A method as recited in claim 20 wherein the retrovirus is a HIV.

25 17. A method for therapeutically or prophylactically treating a retroviral infection in a patient, which comprises administering to the patient a therapeutically or prophylactically effective amount of a compound as recited in claim 1.

18. A method as recited in claim 22 wherein the retrovirus is a HIV.

19. A method for therapeutically or prophylactically treating a retroviral infection in a patient, which comprises administering to the patient a therapeutically or prophylactically effective amount of a
5 compound as recited in claim 2.

20. A method as recited in claim 24 wherein the retrovirus is a HIV.